1641897 Foundational Elements of an Alternate Scientific Approach to Developing Veteran-Centric Precision Cognitive Restoration Interventions

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Abstract

The purpose of this SPiRE is to identify the supports and barriers to scalability of Veteran-tailored iTBS and APT across neurologic conditions, with the longer-term goal of providing an empirical basis for the tailoring of a broader range of cognitive rehabilitation strategies to optimize each Veteran's cognitive function in daily life. After Veterans receive standard cognitive rehabilitation, cognitive impairments often persist and if they do make gains there is limited carry-over to daily function. The tenets of precision neurorehabilitation suggest that tailored interventions will optimize gains and carry-over, but precision-tailoring of cognitive rehabilitation will only be possible if researchers develop and test scalable approaches for identifying, organizing, and analyzing the multitude of Veteran-specific variables driving and influencing treatment responsiveness. This project addresses long-standing scientific barriers to understanding treatment responsiveness, particularly study sample heterogeneity and individual variability. We address study sample heterogeneity by linking Veterans, across TBI and ischemic stroke, according to levels of cognitive impairment. We create a cohort of Veterans with a homogeneous level of cognitive impairment, thereby enabling explication of person-centric factors influencing treatment responsiveness and carry-over to daily function. Advancing understanding of the basic study design elements will be achieved by leveraging our knowledge of intermittent Theta Burst Stimulation (iTBS) and iTBS paired with Attention Processing Training exercises (iTBS + APT). iTBS is advantageous as it robustly improves working memory with just one treatment session. These interventions, together, are advantageous as they can each be tailored to a Veteran's unique cognitive challenges and to target the neural site, unique to each Veteran's neuropathology. These two interventions also directly address cognitive deficits, while simultaneously inducing neuroplasticity in neural regions hampered or impaired by neural injury. We will study Veterans with moderately impaired cognition who, after standard cognitive rehabilitation, continue to struggle with daily life requiring assistance with complex instrumental activities of daily living (IADL). Veterans will participate in a series of two within-subject treatment studies, conducted on two separate days, 2-weeks apart. Veterans will be randomly assigned to first receive a single session of Active iTBS or Placebo iTBS and then they will receive APT paired with their assigned iTBS (Active iTBS + APT vs Placebo iTBS + APT). We will test if diagnosis moderates the effects of these interventions on both immediate and persisting change in cognition. For immediate effects, we use a novel testing battery and for persisting gains we use established and feasible neuropsychological tests as well as an established test of cognitive function during IADL. Results will be used to obtain pilot data and examine feasibility in terms of study attrition relative to Veteran fatigue, mood, and Veteran reports of suitability of key aspects of the study design. These findings will be used to develop a future merit within-subject cross-over study examining the over-arching hypothesis that tailored iTBS and APT applied to a transdiagnostic sample and subsequently matched to a Veteran, according to a biotype algorithm, will result in better functional performance of Veteran-valued IADL.

List of Abbreviations

ABS: Agitated Behavioral Scale

AMPS: Assessment of Motor and Process Skills

APT: Attention Process Training

AUDIT-C: Alcohol Use Disorders Identification Test

BAI: Beck Anxiety Inventory

BRIEF-A: Behavior Rating Inventory of Executive Function

CDW: Corporate Data Warehouse

C-SSRS: Columbia Suicide Severity Rating Scale

CTI: Center for Translational Imaging

DAI: Diffuse Axonal Injury

DAST-10: Drug Abuse Screening Test

DLPFC: Dorsolateral Prefrontal Cortex

DKEFS: Delis-Kaplan Executive Function System

ES: Effect Size

FIM: Functional Independence Measure

fMRI: Functional Magnetic Resonance Imaging

FSS: Fatigue Severity Scale

GIMME: Group Iterative Multiple Model Estimation

IADLs: Instrumental Activities of Daily Living

ImE: Immediate Effects

iTBS: intermittent Theta Burst Stimulation

MCG: Maximum Cognitive Gains

MDS: Modified Digit Span Test

MLM: Mixed-Effects Linear Regression Model

MRI: Magnetic Resonance Imaging

NURIPS: Northwestern University Research Imaging Processing System

PCL: Posttraumatic Stress Disorder Checklist

PE: Persisting Effects

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status

ROI: Region of Interest

TBI: Traumatic Brain Injury

WAIS-IV: Wechsler Adult Intelligence Scale Fourth Edition

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1.0 Study Personnel

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    - Todd Parrish, PhD, Northwestern University
- 2 participating sites: Hines VA, Northwestern University CTI

2.0 Introduction

Each year, 15,000 Veterans incur a new ischemic stroke (stroke) with many of the survivors (32% - 56%) experiencing persisting cognitive impairments [1] and continued cognitive degradation. [2] For the more than 40,000[3] service members with moderate to severe TBI, the rates are similar with about 65% experiencing long-term cognitive impairments. [4,5] Considering the high prevalence of persisting cognitive impairments and that standard stroke and TBI rehabilitation have limited impact in mitigating this fundamental barrier to daily function, this protocol tests the scalability of an approach to effectively and feasibly tailor iTBS and APT to a Veteran's level of cognitive impairment.

Considering that Veterans with the same neurologic diagnosis are not homogenous by brain pathology or recovery patterns [6,7,8,9] and further that Veteran-specific factors such as level of cognitive impairment influence recovery, [10-12] studying treatment responsiveness by diagnosis alone is unlikely to advance understanding of how to tailor interventions to maximize each Veteran's daily function. Thus, we apply our recent work [13] and ideas from the field of mental health [14] to pilot transdiagnostic sampling. More specifically, we create a sample of Veterans with either TBI or stroke who are linked across diagnoses by homogeneous levels of cognitive impairment. Applying our recent work, [13] we use the Functional Independence Measure (FIM) to broadly link Veterans according to the FIM category of moderate cognitive impairment. This category includes individuals with short-term memory problems requiring assistance for problem solving and shifting attention. As this is a broad link, we refine the link according to

neuropsychological tests of cognitive capacity and by testing cognitive function during IADL performance.

This protocol also addresses the need for pilot data to provide the empirical basis for future within-subject cross-over studies. [15] The pilot data will inform the need to account for practice effects while estimating magnitude and duration of treatment effects from a single session of iTBS alone and a single session of iTBS + APT. As iTBS can now be tailored to each Veteran's unique neuropathology [16] and because a single iTBS session can create a potentiated neural environment, [17-21] iTBS is ideal to study alone. For healthy controls, one session of iTBS to the dorsal-lateral-prefrontal cortex (DLPFC), for example, induces gains in executive functioning. [22,23] These immediate effects enhance feasibility of future cross-over studies explicating the constellation of Veteran-specific factors related to a Veteran's responses to multiple interventions. APT is ideal for pairing with iTBS, in part, because APT can be tailored to each Veteran's unique global and domain specific cognitive challenges. The tenets of metaplasticity [24,25] also suggest that APT is ideal because APT is based on principles of exercise-dependent plasticity [26-28]where novel training-exercises across five domains are provided to deliver stimuli of differing intensity. When APT is provided after iTBS, the provision of targeted APT stimuli during the time of iTBS enhanced plasticity is thought to regulate the plasticity ultimately optimizing cognitive gains as well as carry over of training-related gains.

Testing the scalability of an approach to feasibly and effectively tailor iTBS and APT for Veterans across stroke and TBI, advances rehabilitation research by enabling future research addressing the need for an empirical basis to tailor a broad range of cognitive rehabilitation strategies for Veterans across neurologic diagnoses. If the scientific basis for determining how-to feasibly and effectively tailor cognitive restoration interventions remain undeveloped, then Veterans with persisting cognitive impairments will continue to have diminished quality of life and sub-optimal function, ultimately relying on caregivers for performing daily activities.

Rehabilitation research capabilities for complex chronic populations will be advanced by leveraging the study team's collective expertise developing neuromodulatory interventions [9,29-40] and developing methods to mitigate scientific barriers (e.g., imaging motion; [29,31] neural targeting; [16] differential diagnoses; [41] detecting treatment responsiveness; [42-44] study designs and complex analyses [45]). As creating a scientific basis for feasible and effective development of precision Veteran-tailored cognitive restoration interventions has never been explored, the PI has not been funded in this area. Dr. Bender Pape has, however, assembled an interdisciplinary team of experts with established collaborations to address this long-standing need.

3.0 Objectives

Aim 1: Elucidate merits of transdiagnostic sampling. Within the two intervention groups (Group 1: n = 24, Active iTBS and Active iTBS + APT; Group 2: n = 24, Placebo iTBS and Placebo iTBS + APT], we expect that (1i) neurologic diagnosis (stroke, TBI) will not moderate the effect of Active iTBS or Active iTBS + APT on Maximum Cognitive Gain as assessed by the Modified Digit Span (MDS) and the Streamlined AMPS (AMPS).

Aim 2: Obtain pilot data to inform estimation of treatment and practice effects. We will gather pilot data regarding the magnitude and duration of treatment effects as well as MDS and AMPS practice effects. As we anticipate (2i) greater immediate gains in IADL performance (AMPS) after Active iTBS + APT when compared to Active iTBS alone, we will compare Maximum Cognitive Gains (MCG) on MDS with MCG on AMPS between the Active iTBS and Active iTBS + APT groups to determine if MCGs differ in magnitude. We will also determine if

Active iTBS + APT trend lines indicate an additive treatment effect of APT on MDS and/or AMPS. We also anticipate (2ii) some persisting treatment effects and to explicate these effects we will examine effects for Active iTBS and Active iTBS + APT in the short-term (post-pre-treatment), long-term (2 weeks after a session) and cumulatively across treatment sessions. Since the AMPS uses a unique task during each testing interval and MDS uses 1 of 6 alternate test forms, we will determine (2iii) presence and magnitude of practice effects by testing whether prior exposure to MDS or AMPS results in MDS or AMPS gains for Placebo iTBS.

Aim 3: Explicate study attrition by perceived suitability of aspects the study design and the relationship between this perceived suitability and fatigue as well as mood. We will test the ideas that (3i) Attrition rates do not differ by stroke and TBI groups, (3ii) Veterans across stroke and TBI have similar perceptions regarding suitability of the number and type of tests as well as number of study-days, and (3iii) perceived suitability is related to Veteran-reported fatigue and mood.

Aligned with VA RR&D's mission to create knowledge and innovations advancing the rehabilitative health and care of Veterans, this project will scale-up the scientific basis for developing and, ultimately, delivering Veteran-tailored, interventions that improve the aspects of function identified by Veterans across neurologic diagnoses as important to their well-being. For Veterans with moderately impaired levels of cognition who are struggling with daily life, thereby requiring assistance with complex instrumental activities of daily living, this project will explicate critical and practical barriers to developing Veteran-tailored interventions that optimize cognitive function in daily life. The results will be used to design and conduct future merit research examining the over-arching hypothesis that restorative cognitive interventions developed according to transdiagnostic sampling and matched with a biotype algorithm, compared to a diagnosis-based algorithm, result in better functional performance of Veteran-valued IADL.

With additional supplemental funds awarded through the Infinite Hero Foundation administered through Northwestern University Feinberg School of Medicine Department of Physical Medicine and Rehabilitation, two additional aims have been added to this study. With the provide funds, the study will enable all Veteran participants enrolled in the Pilot study to have their baseline fMRI to be collected at Northwestern University Clinical Translational Imaging (NU CTI) center located at Olson Pavilion at 710 N. Fairbanks, Chicago, IL 60611.

Secondly, it will provide additional optional treatment for up to 12 enrolled Veterans with a diagnosis of Traumatic Brain Injury who have enrolled and completed the main study. Participants with the diagnosis of Stroke will not be eligible to participate in the Optional Experimental Treatment sessions.

Additional exploratory aims are:

Aim 4: Optimal Neural Targets for iTBS using Group Iterative Multiple Model Estimation (GIMME) based on ab *a priori* fixed network structure comprised of 12 anatomical nodes associated with cognitive processing. GIMME will be used to identify common, subgroup and unique neural circuits of moderately cognitively impaired participants. For persons with moderate cognitive impairment resulting from TBI, we hypothesize that there will be sub-types of persons with common brain circuitry important to cognition.

Aim 5: Determine immediate gains in working memory and performance of complex IADL after provision of a single session of iTBS targeting to the same location in the L DLPFC that was treated and after a single session of iTBS targeting the optimal GIMME brain target. For persons with moderate cognitive impairment resulting from TBI, we hypothesize that average gains in working memory and functional performance after a single iTBS session site will be

significantly different according to site of stimulation (L DLPFC site, GIMME site).

4.0 Resources and Personnel

- Research will be conducted at the Hines VA Hospital and Northwestern University, Clinical Translational Imaging laboratory (CTI), locate at Olsen Pavilion 710 North Fairbanks, Chicago, IL 20211
- Theresa Bender Pape is the PI. Gwendolyn Kartje is the Co-PI.
- Access to protected health information: All study team members from the Hines VA will have access to protected health information. Consultants and collaborators from outside the VA will not have access to protected heath information.
- Recruitment: Drs. Bender Pape and Kartje, along with trained study personnel, will be involved in recruitment
- Obtaining informed consent: Dr. Bender Pape and trained study personnel will be involved with obtaining informed consent
- Administering procedures: Dr. Bender Pape will administer procedures as well as train study team personnel to administer procedures.
- Data analysis: Zhiping Huo is the team statistician and will lead data analysis with all investigators contributing to the interpretation.
- Due to recent award from the Infinite Hero Foundation awarded to Dr. Theresa Pape, MRIs for this study will be conducted at Northwestern University Clinical Translational Imaging (CTI) laboratory.

5.0 Study Procedures

5.1 Study Design

Recruitment of Veterans will involve a multi-step process to eliminate those who would be at highest risk for adverse events related to study procedures and to identify a cohort of Veterans who meet inclusion/exclusion criteria (Figure 1). NOTE: This is for the primary study, the optional study participation will be for individuals with primary diagnosis of TBI. Veterans with diagnosis of stroke are excluded.

Screening: Identifying and Recruiting Research Candidates:

We will identify a cohort of Veterans from the corporate data warehouse (CDW) by using the ICD codes in the national inpatient and outpatient files available with VA Informatics and Computing Infrastructure. We will identify Veterans with ischemic stroke or TBI admitted to a rehabilitation bed and/or seeking outpatient rehabilitation services (i.e. OT, SLP) from Hines VA in the previous 10 years. We will filter and sort this list to exclude primary diagnoses other than ischemic stroke or TBI, any dementia diagnoses, deaths and enrollment in extended care. We will then re-sort the list by primary and co-occurring diagnoses, gender, age, date of most recent neurologic event, comorbid medical conditions including seizure disorders, by last date of a VA rehabilitation service, and by prescribed medications (by first and last fill date as well as dose). To maximize likelihood of medical stability, Veterans with changes in medications and/or dose within 3-months of list extraction will be excluded. We will use the sorted list to minimize heterogeneity by excluding Veterans with both ischemic stroke and TBI, receiving anti-epileptic medications to control seizures or have a documented seizure three months prior to list extraction, and Veterans with these comorbid medical conditions: congestive heart failure, implanted pacemakers, defibrillators and/or cochlear implants. We anticipate having at least

1,500 Veterans remaining on the list from which we will randomly sample 500 males (250 with ischemic stroke, 250 with TBI) who will each be sent recruitment letters. We anticipate a smaller percentage of female Veterans on the list, therefore we will send a recruitment letter to all female Veterans to reduce risk of results being non-representative across biological sex. The letter will introduce the study and inform Veterans that researchers will be contacting them by telephone, text, and/or email to determine study participation interest. Veterans will be contacted up to 5 times. To determine interest in study participation, male Veterans will be contacted according to the order of the randomized list. During telephone contact, male Veterans expressing interest in study participation will continue with the telephone call to start screening. All female Veterans will be contacted and those expressing interest, will also continue with the telephone call to start screening.

Telephone Screening-Part 1: Stabilization of Functional Recovery and Medical Status:
Considering that the nature, severity and recovery of functional capabilities vary widely within and between ischemic stroke and TBI as well as by sex, the Veteran and/or healthcare surrogate will be asked to report current rehabilitation services (VA, non-VA) and if they experienced a seizure since their last visit to Hines VA. Veterans reporting active rehabilitation services, seizures and/or pregnancy will be excluded. Veterans who report any change in medical status since last medical evaluation will be advised to seek follow up medical evaluation. Veterans remaining eligible will complete a brief iTBS and MRI safety checklist and those without contraindications will proceed to Part-2 of the phone screening. The contraindications identified on the MRI screening form, including but not limited to ferromagnetic or other magnetic-sensitive metals implanted in their head or 30cm of the treatment coil (e.g. implanted electrodes/stimulators, aneurysm clips or coils, stents, medication pumps, intracardiac lines, bullet fragments) or implanted stimulator devised in or near the head (e.g. cardiac pacemakers, deep brain stimulators, cochlear implants, and vagus nerve stimulators), will be excluded.

Telephone Screening-Part 2: Self-Report of Cognitive Impairment:
Part-2 involves a second broad screening of cognitive function based on the Functional Independence Measure (FIM) completed by telephone interview. This incremental cognitive screening approach will circumvent potential diluting effects of including Veterans at extremes of the functional impairment continuum (mild, severe). For the 6-months prior to screening, Veterans requiring minimal or moderate assistance on problem-solving (scores: 3 or 4) and/or minimal assistance or supervision on memory (scores: 4 or 5), will remain eligible. These cut-off points are based on recent research by the study team[6] indicating that Veterans with these scores for these items most likely have short-term memory issues, impeding function, but not long-term memory issues. Veterans and/or healthcare surrogates will be asked to report location of any non-VA emergency room (ER), intensive and post-acute care treatment and for consent to collect these medical records for further screening.

Screening Medical Records:
The VA electronic medical record and any non-VA medical records will be reviewed to confirm completion of rehabilitation services as indicated by inpatient/outpatient therapy reports and notes. Veterans actively receiving therapy services will be excluded. To examine medical stability, we will also confirm that medical status has remained stable for three months (e.g., new seizures, new diagnoses) prior to the records review as well as absence of other exclusionary conditions (e.g., having both TBI and ischemic stroke). We will also review medications to identify Veterans actively receiving pharmacological neurostimulants. These cases will be reviewed by the study neurologist who will consult with the prescribing physician to determine safe withdrawal, via titration. If there is question about safety, then the Veteran will be

excluded. Dictated radiology reports will be reviewed to identify Veterans with ischemic strokes bilaterally who will be excluded.

Medication Review: For participant inclusion and safety, if the participant is prescribed medication know to act on the CNS, an evaluation of cumulative seizure risk and appropriate risk mitigation for each patient according to their prescribed medication profile and relative to self-reported medications, alcohol consumption (AUDIT-C) and substance use (DAST-10) will be evaluated prior to enrollment. In lieu of excluding participants based on the name of any particular drugs or drug classes or limit them to a set, we will follow the procedure as described:

- Clinical experts (e.g., Research Neuropsychiatrist Dr. Alexandra Aaronson, Neuropsychologist Dr. Patrick Riordan, Neurologist and Epileptologist Dr. Vijaya Patil, Neurologist and Stroke Expert Dr. Gwendolyn Kartje) and/or scientific subject matter experts (e.g., TBI expert Dr. Theresa Pape, AUD and SUD expert Dr. Amy Herrold) will review all CNS acting medications for each research candidate/participant.
- CNS acting medications will be reviewed for likelihood of seizure risk according to purpose for which the medication was prescribed, dose, speed of dose change (increase or decrease), combination with other CNS active drugs or other factors potentially contributing to lower the seizure threshold (i.e., sleep deprivation, alcohol consumption, marijuana therapeutic and recreational use).
- The determination (by clinical and/or scientific subject matter experts) of likely or plausible seizure risk will be used to make these decisions:
    - To optimize patient safety and mitigate risk, participant should be titrated off a specific medication(s) or receive a lower dose or alternate medication during study participation:
        - If clinical experts determine that the medication(s) can be safely withdrawn or changed, then participant remains eligible.
        - If clinical experts determine that the medication(s) cannot be safely withdrawn or changed, then the participant will be excluded.

To optimize patient safety and mitigate risk, participant should remain on medication as prescribed and remains eligible for study participation.

For Veterans remaining eligible, medical records will be further reviewed to document biological sex, age, time post ischemic stroke or TBI onset and current co-morbid medical conditions. Dictated radiology reports, as well as other records, will be reviewed to document right vs left cortical and sub cortical ischemic strokes and number of ischemic strokes. Radiology reports as well as clinical notes (e.g., History and Physical) will be reviewed to delineate TBI by etiology including diffuse axonal injury (DAI) and ≥ 1 contusion (e.g., blast, vehicular, assaults) or DAI + ≥ 1 contusion + an anoxic event subsequent to TBI (e.g., respiratory, cardiac). These variables will be examined for use as covariates in analyses.

In-Person Eligibility Confirmation:

Veterans who meet all inclusion/exclusion criteria throughout the phone screening process will be consented for participation and proceed to in-person eligibility confirmation. The final screening step involves in-person testing at Hines VA to confirm that cognitive impairments are moderately impaired in capacity and function as determined by a battery of clinician rated tests including RBANS, WAIS-V, DKEFS, BRIEF, Dot Counting Test and AMPS. We measure cognitive capacity according to neuropsychological tests that correlate with functional

disability.[46,47] We developed a testing battery that can be used to determine study eligibility and that can be feasibly repeated to use as an outcome indicative of persisting cognitive gains (Table 2). The Audit C and DAST-10 will be completed at this time.

Alcohol and Substance Use: As part of eligibility screening, during the in-person screening, the participant will complete the following two self-report tests:

The AUDIT-C is a brief alcohol screening instrument that identifies persons who likely to be hazardous drinkers or have active AUD (including alcohol abuse or dependence). The AUDIT-C has 3 questions and is scored on a scale of 0-12. Each AUDIT-C question has 5 answer choices valued from 0 points to 4 points. In men, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. In women, a score of 3 or more is considered positive. Generally, the higher the score, the more likely it is that a person's drinking is affecting his or her safety.

The DAST, a NIDA CTN common data element, is a brief, self-report instrument for population screening, clinical case finding and treatment evaluation research. The DAST-10 is a 10-item self-report instrument that has been condensed from the 28-item DAST. Scores range from 0 to 10 with scores of 1-2 being considered low level problems that should be monitored with re-assessments periodically whereas further evaluation is indicated with a score of 3 or more.

Persons with alcohol use disorder (AUD) and/or substance use disorder (SUD) diagnoses confirmed by clinical and/or scientific experts (e.g., Research Neuropsychiatrist Dr. Alexandra Aaronson, Neuropsychologist Dr. Patrick Riordan, Neurologist/Epileptologist Dr. Vijaya Patil) and/or scientific subject matter expert (e.g., Dr. Amy Herrold) will be excluded.

Persons who do not have AUD or SUD but do consume alcohol and/or use elicit substances at a level, as determined by clinical and/or scientific experts (e.g., Research Neuropsychiatrist Dr. Alexandra Aaronson, Neuropsychologist Dr. Patrick Riordan, Neurologist/Epileptologist Dr. Vijaya Patil) and/or scientific subject matter expert (e.g., Dr. Amy Herrold), likely to elevate seizure risk (i.e., hazardous level plausibly lowering of seizure threshold) will be excluded.

If a participant screens positive on the AUDIT-C (Men score of 4 or more, women score of 3 or more), then they will be referred to their clinical care team for further evaluation and clinical management.

If a participant scores 1 to 2 on the DAST, then substance use will be monitored by having researchers re-administer the DAST on each study day.

If at any time a participant scores a 3 or more on the DAST, then they will be referred to their clinical care team for further evaluation and clinical management.

Figure 1. Four Step Screening Process: Summary of Exclusion Criteria by Steps

Step 1: Identifying and Recruiting Research Candidates

Exclude:
- Have BOTH TBI and ischemic stroke
- Primary Diagnosis other than TBI or ischemic stroke
- Any Dementia diagnosis
- Reside in an extended care facility
- < 2-years post TBI or ischemic stoke
- Anti-epileptic medications for seizure activity
- Seizure 3 months prior to list extraction
- Contraindications to iTBS and MRI
- Change in medication or Dose in prior 3 months

Step 2: Telephone Screening

Exclude:
- Receiving therapy services, active seizures and/or pregnancy
- FIM scores 6-months prior: Problem Solving: < 3 or > 4 **OR** Memory: <4 or > 5

Step 3: VA and Non-VA Medical Records Review

Exclude:
- Any previous exclusion criteria
- FIM scores change
- Pharmacological neurostimulants cannot be safety withdrawn
- Bilateral ischemic strokes

Step 4: In-person Testing

Exclude:
- Mildly or Severely impaired cognitive capacity OR function
- RBANS < 70
- DOT E-score ≥ 17
- BRIEF-A: Negativity ≥ 6; Infrequency ≥ 3; Inconsistency ≥ 8

For this within-subject placebo-controlled partially-blinded treatment protocol (Fig 2), we will enroll 48 medically stable Veterans with stabilized recovery trajectories after a stroke or a TBI and who have a homogeneous level of moderately impaired cognitive function persisting after standard rehabilitation.

An equal number of Veterans with stroke/TBI (24-stroke; 24-TBI) will be enrolled, but we will over-sample females (Figure 2). For each iTBS group to include an equal number of Veterans with stroke/TBI, Veterans will be randomly assigned by diagnostic groups, to receive Active iTBS or Placebo iTBS. To measure immediate effects (ImE), an equal number of Veterans with stroke/TBI within each iTBS group will be randomly assigned to be tested with the Modified Digit Span (MDS) or AMPS, three times at 30 min intervals. Persisting effects (PE) tests will be administered to all participants at five timepoints including prior to and after Active iTBS or Placebo iTBS and 2-weeks later prior to the 2nd intervention, where all Veterans receive APT paired with their assigned iTBS (Active *iTBS + APT or Placebo iTBS + APT).* The alternate ImE test is then administered three times at 30 min intervals, followed by re-administration of all PE tests. Two weeks later, all PE tests are administered a 5th time (B4). ImE and PE measures are used to define magnitude and duration of cognitive change. Randomization (SAS Proc Plan) will be managed by one un-blinded researcher who will not provide interventions or conduct testing.

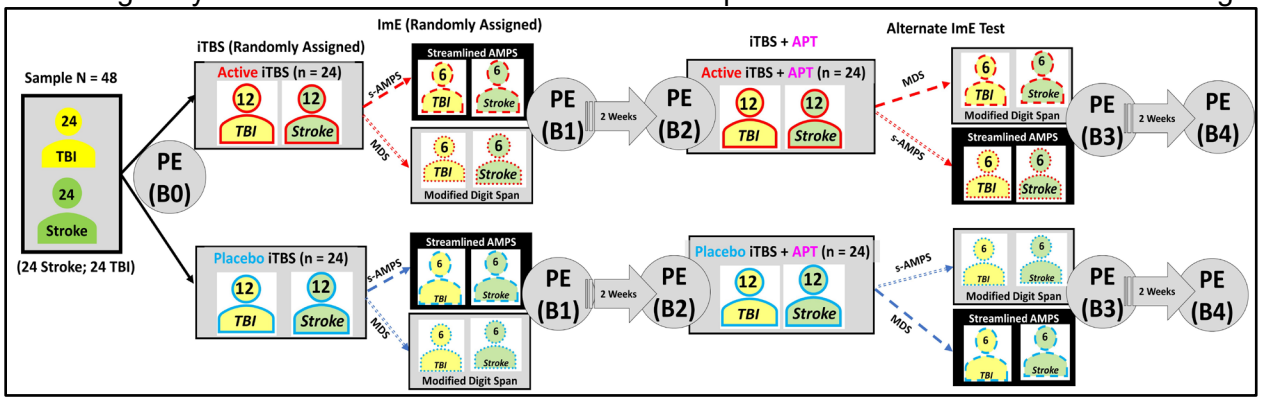


Figure 2. Study Design (**ImE =** Immediate Effects Tests: **AMPS** = AMPS or **MDS** = Modified Digit Span; **PE =** Persisting Effects Tests for all participants; **Study Day-1:** Obtain Covariates and Treatment preparation information; **B0 =** Pre-Study-Day-2; **B1 =** Post-Study-Day-2; **After 2-Weeks B2 =** Pre-Study-Day-3; **B3 =** Post-Study-Day-3**; After 2-Weeks B4 =** Study-Day 4)

Study-Day 0 (In Person Eligibility Screening) (2-3 hours)

1. Complete questionnaires and testing
    a. Audit-C and DAST-10

b. Testing questionnaires
c. Demographic information collection

Study-Day 1 (~5 hours) (may occur over 2 days):

1. Complete tests/questionnaires that are not repeated. Some are collected for use as covariates (Table 2) and some are needed for treatment preparation.
    a. Baseline testing battery
    b. APT Baseline
    c. fMRI-to be completed at NU CTI
    d. Motor Threshold
    e. Baseline EEG*
2. Rating suitability of the number and types of tests 1-3.
   *EEG to be completed prior and reviewed by physician prior to Motor Threshold

Study-Day 2 (4 days after Study Day 1)(~8 hours):

1. PE testing battery
2. A single session of Active iTBS or Placebo iTBS
3. Randomly assigned ImE test (MDS or AMPS), administered 3-times at 30 min intervals, each interval includes 5 to 15 min of rest).
4. PE testing battery
5. Suitability ratings 1-3

Study-Day 3 (2 weeks after Study Day 2)(~8 hours):

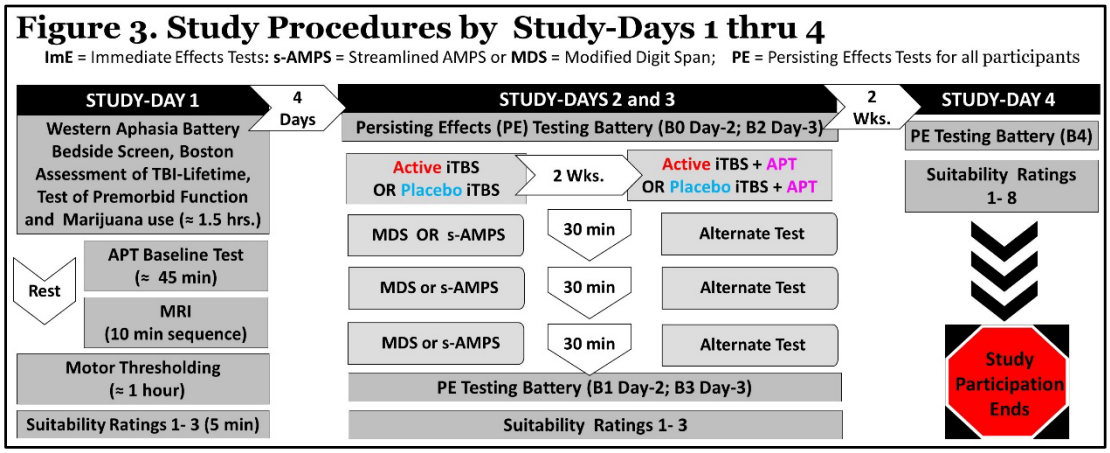
1. PE testing battery
2. Single session Active iTBS+ APT or Placebo iTBS+APT
3. Alternate ImE test (MDS or AMPS) three times at 30min intervals
4. PE testing battery
5. Suitability ratings 1-3

Study-Day 4 (2 weeks after Study-Day 3) (~2.5 hours):

1. PE testing battery
2. Suitability rating 1-8

Optional Study for Participants with diagnosis of TBI only- Day 5 (to occur within 2 weeks of Day 4, can occur on same day as Day 4) (~2 hours)

1. Single session of Active iTBS at GIMME site of stimulation
2. ImE test: MDS, one time only
3. ImE test: AMPS, one time only



Interventions. All iTBS sessions will be **double-blinded,** but APT exercises ***will not*** *be blinded.* For Active iTBS and Placebo iTBS, the left DLPFC using the Resting Network Mapping algorithm.[60,93] .

fMRI (neuroimaging)- Functional MRI (fMRI) measures will be collected at Baseline. The fMRI measures will include structural imaging, 20 minutes of resting-state fMRI, diffusion tensor imaging (DTI) and an Arterial Spin Labelling Sequence (ASL). Participants will be in the MRI for approximately 55 minutes. fMRI scanning, for all participants, will take place at Northwestern University's CTI in the Olsen Pavilion located at 710 N Fairbanks, Chicago, IL 60611.

Veterans will be responsible for transportation to the CTI, however parking vouchers will be provided at not cost to the participant. Parking is available at the Northwestern Memorial Hospital parking garage located across from the Olsen Pavilion. Research staff will be present on day of scan and available to provide assistance.

Scanning will take place on a Siemens Prisma 3.0 T MRI scanner equipped with a 64-channel head/neck coil. A high-resolution 3D MP-RAGE T1-weighted sagittal anatomical scan (voxel size = 0.8 mm isotropic resolution; 224 sagittal slices) will be collected for each participant. Resting state BOLD data will be collected using T2* weighted EPI with a TR=0.5s, TE=25ms, flip angle of 48^{o}, and 2mm isotropic voxels and a multiband factor of 8. Rest data will be collected while the subject views a fixation crosshair. The DTI data will use a two shell (64 directions per shell) acquisition with diffusion values of 1000 mm^2/sec. The acquisition will collect 1.5mm isotropic voxels with a TR=4500, TE=62ms and a multiband factor of 4, and 96 slices.

The collection of the fMRI data will be directed by Dr. Todd Parrish. fMRI data collected at CTI will be de- identified and uploaded to Northwestern University Research Image Processing System (NURIPS), an online collaborative research environment for securely storing, managing, analyzing and sharing de-identified medical imaging, associated data (e.g., behavioral), and results from advanced customizable processing pipelines. NURIPS is supported by both Northwestern University IT and Feinberg School of Medicine IT and takes advantage of the NU high performance computing cluster, Quest. NURIPS is a secure environment that supports the latest NU policy and procedures for encryption of data during transit and rest, provides granular project level access controls with varying permissions based on user groups, and allows non-NU collaborators access once they obtain an affiliate NetID. All data are backed up and have restore points that go back for 30 days. Once the data is uploaded to NURIPS, a copy will be

downloaded onto Hines VA secure research servers for storage on \\v12.med.va.gov\v12\hin.

Motor Threshold Testing & Brain Mapping Site of Stimulation
Stimulation intensity that will be used in iTBS will be determined by collecting each participant's motor threshold (MT) using the finger representations of the motor cortex. The consensus in the literature is that iTBS can be safely provided at 80% of active motor threshold (AMT). Since there is more within and between subject variability with AMT (e.g, different gripping strengths), relative to resting motor threshold (RMT), scientifically the RMT is preferred. There is also recent evidence that motor threshold estimates using RMT and AMT are equivalent.[98] This means that treatment intensity, based on these two MT estimation procedures, would be equivalent, we will use RMT to estimate MT and compute treatment intensity. Thus, the standard iTBS parameters will be used in this trial to maximize safety. iTBS will be provided at 80% of RMT.

In order to determine motor threshold, a structural brain image of the participant is needed. Therefore, eligible participants will undergo an fMRI scan in order to obtain a structural brain image also referred to as the participant's 3D-MPRAGE T1 volume. This T1 image will be loaded into the Localite TMS Neural Navigator system which is a Magventure compatible and portable neuronavigational system. Based on the T1 image, the right motor cortex will be initially targeted to determine MT. Single pulse TMS will be applied to the optimal scalp location ('hot spot') to activate the abductor pollicis brevis (APB) in the hand, that functions as an abductor of the thumb, on the left hand to determine the RMT, or the lowest stimulus intensity necessary to produce MEPs of peak-to-peak amplitude ≥50μV in 5 of 10 subsequent trials. MT is lowest in intrinsic hand muscles and higher in more proximal muscles. The same data will be collected on the opposite hemisphere for comparison measures. MEPs will be recorded using surface EMG electrodes. Data will be stored on the computer for offline analysis. The Magventure C-B60 coil will be used to deliver single TMS pulses for MT determination. All participants, regardless of group randomization will receive MT testing and thus will receive some stimulation. The motor threshold will be measured only at Baseline.

We will use each Veteran's MT, an indicator of cortical excitability, as the benchmark for determining iTBS intensity for each participant (iTBS intensity will be 80% of each subject's RMT). This intensity will be maintained throughout study participation.

iTBS will be delivered with the Magventure MagProX100 with MagOption stimulator and Cool Coil B65. Active iTBS will be provided using active setting (A) at 80% of each Veteran's resting motor threshold. Placebo iTBS participants will not receive any stimulation as the coil will be switched to placebo (P) setting. To maintain double-blind in A and P settings, Veterans and researchers wear headphones connected to a sham noise generator.

For **APT**: 30 min of training exercises, 10 min metacognitive training, and 5 min of functional goal setting. Study-Days 2 or 3 sessions will each include novel exercises. For metacognitive training, the Veteran will be instructed on how to use strategies to self-regulate or to "think about his or her own thinking" and to self-monitor while performing an activity and efficiently allocate his or her cognitive resources. Goals will then be set to implement the strategy in the Veteran's daily life.

iTBS will be delivered with the Magventure MagProX100 with MagOption stimulator and Cool Coil B65. Active iTBS will be provided using active setting (A) at 80% of each Veteran's resting motor threshold. Participants randomized to active iTBS will receive stimulation at the left DLPFC at 80% RMT. 80% RMT is the intensity most commonly used and cited in the literature and has been shown to be safe[26]. The right DLPFC will be marked in the TMS Localite

Navigation system for each participant. The navigation system will provide target guidance and will help the researcher to position the coil very precisely in reference to the participant's brain. The neuronavigation system will be used every iTBS session to ensure reproducibility and consistency at the stimulation site.

For the Optional Study: The site of stimulation will be determined by the GIMME modeling. Optimal brain target is identified through GIMME modeling, which is a directed functional connectivity modeling approach based on iterative model optimization.[96,97]

Potential Risks:

***Physical*:** The experimental intervention of iTBS being provided is a patterned form of rTMS. The biggest concern for transcranial magnetic stimulation (TMS) is seizure induction. Other known side effects of rTMS include headache, dizziness, tinnitus, nausea, neck pain, or scalp burns.[52] Side effects reported to date for iTBS include sweating, feeling dizzy, [53] neck pain, mild decrease in diastolic blood pressure, headache, [54] discomfort/mild tingling sensation, [55] occasional local pain or discomfort during stimulation, and isolated, transient, non-pulsatile, left-sided tinnitus.[56] Additionally, there is risk of equipment malfunction. The Magventure MagProX100 with MagOption stimulator and Magpro Cool Coil B65 or one of the coils may malfunction which may result in harm to the patient.

Participation in the AMPS requires the Veteran to complete a variety of physical tasks that may be challenging to complete. There is a risk of injury depending on the type of task the Veteran identifies as valuable to complete (e.g. burns, laceration, falls).

Psychological: Participation in the study outcome measures, including self-report (i.e. PCL), observational (i.e. ABS), neuropsychological (i.e. DKEFS, WAIS-IV), cognitive capacity and function outcomes (i.e. AMPS, RBANS), effort testing (i.e. DCT) structured interview data (AMPS) and safety outcomes (Data Safety Monitoring Scale), involves minimal risks and discomforts. The risks for the Veteran include frustration, agitation, anxiety, fatigue, and possible trigger of PTSD symptoms.

fMRI: There are no known risks associated with fMRI when individuals are appropriately screened, except some people have experienced discomfort in trying to remain still. MRI is not safe when specific ferromagnetic materials are present in the body (i.e. metal fragments in brain/skull, metal surgical clips, etc). Some people have been noted to be anxious or claustrophobic during the scan. The MRI scanner makes loud banging noises during scanning.

EEG: The self-adhesive used with surface EEG electrodes may produce minor irritation of the skin. The possibility of irritation will be minimized by applying gel to the skin prior to electrode placement and by cleaning the skin with alcohol before and after the application of the electrodes. If there is irritation, then additional gel will be used on future applications. There is also the possibility of an allergic reaction to the electrode gel. If the participant is allergic to the gel, then the response plan is to use an alternative gel. If the scalp is red to the extent beyond minor irritation, then the response will be to substitute the standard EEG electrode placement with conductive plastic electrodes and the standard electrode placement will still be used.

Protection Against Risk:

Physical: In order to minimize the risk of harm from seizure should one occur during iTBS, motor thresholding and all treatments will be provided in a room within the hospital's Rapid Response

area. If Veterans show any signs of seizure or other adverse reaction, study team will contact the Hines Rapid Response Team via Rapid Response call button or via phone. Once the Rapid Response Team arrives, they will assume responsibility for carrying out all emergency procedures.

The treatment room is equipped with a crash cart, defibrillator, pyxis machine and all equipment needed to monitor vital signs. The Rapid Response team is triggered via phone call using the phone physically located in this room. There is also an accessible code button within 20 feet of this room. Researchers have completed training with the Rapid Response and Code teams on activating these emergency systems as well as monitoring and caring for the subject while awaiting arrival of the Rapid Response or Code teams.

To prevent hearing loss, all Veterans will wear headphones during the iTBS intervention. For Veterans who are receiving placebo iTBS, the sham noise generator will be set to a sound level that is within the normal hearing range to prevent hearing damage.

The following safety indicators will be tracked at each study day: blood pressure, heart rate, fatigue, tinnitus, sleep, dizziness, nausea, vomiting, confusion, seizure, headache, and neck pain. Change from baseline is rated according to severity and for each severity rating there is a specified medical response to be followed. The ratings are on a scale of 1 to 5 with a higher number indicating more deleterious change.

To minimize the risks of iTBS, the following rules will apply for pausing, stopping or rescheduling iTBS:

Rules for Pausing treatment to Evaluate Need to Change iTBS Treatment Protocol:

1) Any seizure
2) Skin break-down on scalp at site of TMS
3) Constant headaches that do not resolve with acetaminophen
4) Suicidality response on C-SSRS is 2 or higher
5) A composite score of visuomotor processing speed assessments that falls below 2 standard deviations from the mean.

Rules for Stopping iTBS Treatment/Study Participation:

1) Shock (of any etiology),
2) Any seizure activity that study epileptologist deems as categorizing someone as unsafe to continue iTBS
3) A participant who previously agreed during consenting procedures to stop taking amphetamine and non-amphetamine/methylphenidate CNS stimulant medications reports initiating taking these medications, and does not wish to forgo CNS stimulants for remainder of study participation
4) Any participant experiences a change to their prescribed medications, either initiating a new mental health medication or experiencing a prescribed change in dose for mental health reasons during study participation
5) Participants with a positive urine pregnancy screen or report new pregnancy (for females)

Rules for Rescheduling Treatment Session

1) Participant reports taking CNS stimulants (non-amphetamine/methylphenidate and/or amphetamine-based stimulants), but express willingness to discontinue CNS stimulants to enable continued study participation
2) Subject reports sleep disruption and epileptologists determine that iTBS should not be provided during scheduled visit, but could be provided after sufficient sleep is achieved.

To prevent equipment malfunction, the equipment will be inspected before and after each iTBS session. Manufacturer guidelines will be followed according to maintenance and useful life of the device. Should any equipment appear broken or have loss of integrity, the equipment will not be used until it is inspected by the biomedical engineering department at Hines VA Hospital and the Magventure service representatives.

Dr. Theresa Bender Pape has secured an FDA Investigational Device Exemption (#G150119) for the intended use of this device (Magventrue MagPro X100) for persons with mild TBI. Safety protocols and total amount of stimulation are the same as the currently approved FDA IDE. An FDA Investigational Device Exemption has been secured dated 1.12.2022., G210364. The FDA has found that iTBS does not present a risk to the health, safety, or welfare of individuals with brain injuries, and does not cause seizures at a rate of stimulation used in the current research design for persons without brain injury. However, it is noted that the risk of causing a seizure in persons with brain injuries or ischemic stroke is not known but it is possible that iTBS could cause one or more seizures.

In event of a seizure, the following response will be administered:

- Within 0-5 Minutes: Stabilization phase, initiated immediately upon patient demonstrating seizure-like activity
    - Stop stimulation
    - Notify RRT (Rapid response team) and MD experienced in seizure management
    - Basic Seizure First Aid will be provided by research staff until RRT arrives:
        - Ensure patient in safe position
        - Stabilize patient (airway, circulation, breathing, neurologic exam)
        - Track time
        - Obtain vital signs (BP, HR, RR and SpO2)
        - Vast majority of seizures are self-limited within 5 minutes1
- Within 5-20 minutes: Initial therapy phase
    - RRT arrives within 5-10 minutes of seizure onset and assumes responsibility for carrying out all emergency procedures. Research team will notify RRT of intervention and patient's vital signs thus far to facilitate coordination of care. RRT initiates the tasks below; the time frame for these tasks may run into next phase.
        - O2 administration if SpO2 <90%
        - Cardiac monitoring
        - Glucose assessment
    - MD will assess the situation and prescribed benzodiazepine will be administered by RRT if indicated. Respiratory support will be provided by RRT if necessary.
- Within 20-40 minutes-Second therapy phase

- Emergency medical services continues individualized care.
- Following termination of seizure activity, medical evaluation completed by emergency room physician, Dr. Patil, covering MD or on call Epilepsy physician

RRT will determine timing of transportation to ER once subject is determined to be stable for transport.

The stimulating coil will be used on multiple Veterans. To prevent the spread of contamination from one Veteran to the next, the coil will be disinfected and sanitized after every iTBS session.

To further ensure participant safety, all female Veterans will submit to a urine pregnancy screen at baseline. If the urine screen is positive for pregnancy, the Veteran will be excluded from participation.

To prevent injury during participation in AMPS assessment, all Veterans will be supervised by an AMPS certified Occupational Therapist.

Psychological: If the participant exhibits frustration or fatigue, then the response plan is to pause testing and comfort them. Testing will be resumed after the Veteran exhibits signs of reduced frustration. Should the Veteran experience PTSD symptom trigger during any treatment or testing, the response plan will be to immediately consult with the Hines Mental Health Service and follow their recommendation.

To monitor depression, specifically suicide ideation, the C-SSRS will be administered at baseline and repeated as part of each battery assessment. Administration of the C-SSRS will be as defined:

- At each C-SSRS administration, all participants will complete the first two questions, #1 'wish to be dead' and # 2 non-specific active suicidal thoughts'
- For participants answering questions 1 and 2 affirmatively, then researchers will administer the entire C-SSRS and
  - <u>For Lifetime:</u> If the C-SSRS results indicate that a participant endorses having had suicidal ideation or a suicide attempt in the past, then the participant will be asked if their mental health provider(s) are aware of this.
    - If provider(s) are aware, and patient denies all suicidal ideation/behavior at the present time (i.e., past month), participant will be allowed to proceed in the study.
    - If the participant is not actively engaged in mental health treatment, then the research psychiatrist will be contacted to determine what form of psychiatric care is warranted at this time (e.g., contacting of emergency authorities, escorting participant to intake for scheduling an outpatient evaluation).
    - If they are engaged in mental health treatment and their mental health providers are not aware of past suicidality, then researchers will inform the mental health provider(s) of past suicidality and the determination of study eligibility will be made based on the recommendations of these mental health providers
  - <u>For Past Month:</u> If at any point during the C-SSRS subject endorses passive suicidal ideation at the present time (wish to be dead in past month), then:
    - The study team's psychiatrist will be contacted to evaluate subject symptom acuity, and:

- If the participant is actively engaged in mental health treatment, then the study team's psychiatrist will discuss the case with the participant's mental health provider who will determine the safety of subject continuing in the study.
- If the participant is not actively engaged in mental health treatment, then the research psychiatrist determine what form of psychiatric care is warranted at this time (e.g., contacting of emergency authorities, escorting participant to intake for scheduling an outpatient evaluation).

If subject endorses any active suicidal ideation (C-SSRS questions 3 through 5) OR recent suicidal behavior (i.e., preparatory behaviors, self-harm, recent suicide attempt) subject will be excluded from study AND study team psychiatrist will be contacted to evaluate subject and determine what form of urgent psychiatric care is warranted at this time (e.g., contacting of emergency authorities, contacting of subject's mental health provider(s)).

fMRI: Prior to enrollment into the study, prescreening is completed with research staff to evaluate the Veteran's compatibility and safety for having an MRI related to the presence of ferromagnetic material in the body (i.e. metal fragments in brain/skull, metal surgical clips, etc). Prior to the MRI, the MRI safety checklist is repeated (from screening) and reviewed for contraindications. Some people have been noted to be anxious or claustrophobic during the scan. In the pre-screening process, it is asked and reviewed if the Veteran has any issues with claustrophobia or anxiety in closed spaces. The Veteran may be recommended to not participate in the study if it is unknown. The MRI scanner makes loud banging noises while taking a measurement, so either ear plugs, or specially designed headphones will be used to reduce the noise. The researchers will be in communication with the participant through an intercom system to ask how the participant is doing. The earplugs should not get in the way of communicating with the researchers. The participant can speak to the technician by talking out loud. If at any time, or for any reason, the participant wishes to stop the exam, he may do so by squeezing a rubber ball.

This protocol will involve the vulnerable population of persons with cognitive disabilities and may involve persons lacking decisional capacity. Due to the nature of the medical condition of the Veterans recruited, the healthcare surrogate (legally authorized representative) may be the person providing informed consent for research participation. All Veterans will provide assent in addition to the informed consent if necessary to obtain consent from the healthcare surrogate. In order to develop treatments to improve cognitive function, individuals with cognitive impairment related to ischemic stroke or TBI must participate in the current study design.

5.2 Recruitment Methods

48 Veterans will be enrolled.

We will identify a cohort of Veterans from the corporate data warehouse (CDW) by using the ICD codes in the national inpatient and outpatient files available with VA Informatics and Computing Infrastructure. We will identify Veterans with ischemic stroke or TBI admitted to a rehabilitation bed and/or seeking outpatient rehabilitation services (i.e. OT, SLP) from Hines VA in the previous 10 years. We will filter and sort this list to exclude primary diagnoses other than ischemic stroke or TBI, any dementia diagnoses, deaths and enrollment in extended care. We will then re-sort the list by primary and co-occurring diagnoses, gender, age, date of most recent neurologic event, comorbid medical conditions including seizure disorders, by last date of a VA rehabilitation service, and by prescribed medications (by first and last fill date as well as dose). Once a list of possible participants is generated, a chart review encompassing CPRS, JVL and

CAPRI will be conducted to review for pre-screening of eligibility, including, but not limited to, medication (and recent changes (and recent inpatient services for medical stability. We will use the sorted list to minimize heterogeneity by excluding Veterans with both ischemic stroke **and** TBI, receiving anti-epileptic medications to control seizures or have a documented seizure three months prior to list extraction, and Veterans with these comorbid medical conditions: congestive heart failure, implanted pacemakers, defibrillators and/or cochlear implants. We anticipate having at least 1,500 Veterans remaining on the list from which we will randomly sample 500 males (250 with ischemic stroke, 250 with TBI) who will each be sent recruitment letters. We anticipate a smaller percentage of female Veterans on the list, therefore we will send a recruitment letter to all female Veterans to reduce risk of results being non-representative across biological sex. The letter will introduce the study and inform Veterans that researchers will be contacting them by telephone, text, and/or email to determine study participation interest. Veterans will be contacted up to 5 times. To determine interest in study participation, male Veterans will be contacted according to the order of the randomized list. During telephone contact, male Veterans expressing interest in study participation will continue with the telephone call to start screening. All female Veterans will be contacted and those expressing interest, will also continue with the telephone call to start screening.

A flyer will be created to provide to VA clinicians to provide to potential candidates or caregivers and post in approved common areas. We will also screen medical records of Veterans in relevant clinics, such as Neurology, which will be accessed through CPRS.

Veterans will receive $100 compensation for completed participation in the study protocol. Compensation will be disbursed via Electronic Funds Transfer (EFT) using the veteran's preferred method (ex. Direct Deposit or Direct Express Debit card, etc.). Veterans who are unable to utilize this option may not be able to receive compensation. Participants will have an opportunity to discuss this option prior to consenting to participate in the study. The participant will be advised payment will take up to 10-14 days to show on their provided account.

There is no additional compensation for participation in the optional study treatments.

Parking vouchers will be provided at the time of visit to Northwestern University CTI. As long as participant parks in designated Northwestern Memorial parking garage, they will receive a voucher for the parking. Map and directions to the appropriate lot will be provided prior to the appointment.

5.3 Informed Consent Procedures

No informed consent waivers will be obtained.

A partial HIPAA waiver will be requested for recruitment and initial screening.

The consent process will be conducted in English by trained research staff at Hines VA in a designated, private treatment room. Because some of the assessments used are currently only validated in English, the Veteran, and as necessary, the healthcare surrogate must be fluent in written and verbal English. If either of these individuals cannot speak English, the Veteran will be excluded from the study. The Principal Investigator will be available for further discussion or questions regarding research participation as needed during the informed consent meeting.

Informed consent documents will be made available to potential participants, and as applicable the healthcare surrogate, prior to the informed consent meeting. Research participants have

access to research staff to assist with any questions or concerns until understanding is achieved to the judgment of the individual asking the question. If a potential participant refuses, no further contact will be made. If the Veteran, or healthcare surrogate with assent of the Veteran, consents to the study, a copy of the signed consent is provided, a copy is filed with the Hines IRB, and the original Informed Consent is placed in a research binder and maintained in a locked file cabinet at Hines VA. Once the informed consent process is completed, a note will be documented in CPRS (Hines Electronic medical record system) and the Veteran will be flagged as a research participant.

The optional study procedures will be included in the informed consent, if the participant is eligible to participate in the optional procedures, the researcher will provide information about the additional treatment sessions. The participants will initial their assent or dissent to participation in the optional study treatments. It will be communicated in the informed consent process that they can change their mind in participation of the additional treatments and participation at any time. If they chose to opt out of the participation, documentation will be made in the participants study binder and CPRS. If they chose to opt in after initially declining, a new Informed consent will be signed and dated, and documentation will be made in participants study binder and CPRS. Participation in the optional study procedures will not have impact in the participation in the primary study.

Northwestern Specific Procedures: All participants will sign a Northwestern IRB approved consent form and a VA approved consent acknowledging participation in a VA sponsored study. Copies of the Northwestern signed consent forms and original VA consent forms will be mailed via chain of mail custody to the Clinical Research Coordinator at the Hines VA. Copies of the VA consent will be provided to the Hines IRB. Consent documents will be stored in locked file cabinet, behind a locked door at the Hines VA Building 1, Room B317. A copy of the signed Northwestern consent form will be provided to NU through the Study Tracker system.

5.4 Inclusion/Exclusion Criteria

Table 1. Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Diagnosis of TBI or Ischemic Stroke • 2-10 years post neurologic event having completed rehabilitation • Age 18 - 80 years old • Medically stable • Fluent in English • Moderately impaired cognitive function as defined by AMPS Processing sub-scale measures falling below 1.0 logits • Moderately impaired cognitive capacity as	• Have BOTH TBI and Ischemic Stroke • Intracranial lesions or hemorrhagic stroke • Other primary neurologic diagnosis • Any dementia diagnosis • History of/or symptoms of psychotic spectrum disorders (i.e., bipolar, schizophrenia) • Persons with alcohol use disorder (AUD) and/or substance use disorder (SUD) diagnoses confirmed by clinical and/or scientific experts • Reside in an extended care facility • Less than 2 years post TBI or ischemic stroke • Anti-epileptic medications for seizure activity

defined by having two or more scores falling ≥1 standard deviation below age normed expectations on: the RBANS index scores, DKEFS Color-Word Trials 3 and 4 scale scores, and/or WAIS-IV Digit Span scaled score	• Seizure within the past 3 months or active seizure • Contraindications to MRI/iTBS such as ferromagnetic or other magnetic sensitive metals implanted in their head or with in 30cm of the treatment coil or implanted devices in or near the head • Medication changes within 3 months of starting participation • Currently receiving therapy services • Pregnancy • FIM scores for problem solving <3 or >4 OR memory <4 or >5, or changes in FIM scores during screening process • Neurostimulants that cannot be safely withdrawn • Bilateral ischemic stroke • Mild or severe impairments in cognitive capacity or cognitive function • CHF, implanted pacemakers or defibrillators, or cochlear implants • Heart valve with metallic materials • Questionable test validity as indicated by DOT (E-score ≥ 17) or BRIEF (Negativity ≥ 6; Infrequency ≥ 3; Inconsistency ≥ 8) • RBANS Total Scale < 70
OPTIONAL STUDY INCLUSION/EXCLUSION CRITERIA	
Inclusion Criteria	**Exclusion Criteria**
• Diagnosis of TBI • 2-10 years post neurologic event having completed rehabilitation • Age 18 - 80 years old • Medically stable • Fluent in English • Moderately impaired cognitive function as defined by AMPS Processing sub-scale measures falling below 1.0 logits • Moderately impaired cognitive capacity as defined by having two or more scores falling ≥1 standard deviation below age normed	• Have BOTH TBI and Ischemic Stroke • Intracranial lesions or hemorrhagic stroke • Other primary neurologic diagnosis • Any dementia diagnosis • History of/or symptoms of psychotic spectrum disorders (i.e., bipolar, schizophrenia) • Persons with alcohol use disorder (AUD) and/or substance use disorder (SUD) diagnoses confirmed by clinical and/or scientific experts • Reside in an extended care facility • Less than 2 years post TBI or ischemic stroke • Anti-epileptic medications for seizure activity • Seizure within the past 3 months or active seizure

	expectations on: the RBANS index scores, DKEFS Color-Word Trials 3 and 4 scale scores, and/or WAIS-IV Digit Span scaled score	• Contraindications to MRI/iTBS such as ferromagnetic or other magnetic sensitive metals implanted in their head or with in 30cm of the treatment coil or implanted devices in or near the head • Medication changes within 3 months of starting participation • Currently receiving therapy services • Pregnancy • FIM scores for problem solving <3 or >4 OR memory <4 or >5, or changes in FIM scores during screening process • Neurostimulants that cannot be safely withdrawn • Bilateral ischemic stroke • Mild or severe impairments in cognitive capacity or cognitive function • CHF, implanted pacemakers or defibrillators, or cochlear implants • Heart valve with metallic materials • Questionable test validity as indicated by DOT (E-score ≥ 17) or BRIEF (Negativity ≥ 6; Infrequency ≥ 3; Inconsistency ≥ 8) • RBANS Total Scale < 70

5.5 Study Evaluations

Data collected will include data related to safety in the administration of the experimental intervention, iTBS, immediate and persisting effects of the intervention, and acceptability of the intervention based on Veteran fatigue ratings, mood, agitation, and measures of Veteran-perceived suitability.

Electronic Medical Records: Screening procedures involving a review of the Veteran's medical records to screen for eligibility and safety to participate. A HIPAA waiver will be requested to provide the research clinician access to the Veteran's medical record to screen for study eligibility based on the approved inclusion/exclusion criteria. If a Veteran is receiving care outside the VA, a medical records request will be initiated to obtain necessary records to support inclusion/exclusion criteria screening. Medical records will also be screened for documentation by a physician that the Veteran lacks decision making capacity. If the Veteran continues to meet all inclusion/exclusion criteria after telephone screening and medical record review, the Veteran will be scheduled for in person eligibility screening and either the Veteran or healthcare surrogate with assent of the Veteran will provide informed consent.

Self-report, Observational, Neuropsychological, Cognitive Capacity and Functional Outcomes, Effort Testing, and Structured Interview Data: In person eligibility confirmation testing, study outcomes and covariate data will be collected for each Veteran during screening, at enrollment, and throughout their participation in the study.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) will be used to broadly assess a range of cognitive domains (e.g., Learning/Immediate Memory, Language, Attention) whereas the Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span subtest10 will be used to measure working memory. The Delis-Kaplan Executive Functioning System (DKEFS) Color-Word Interference subtest will be used to measure processing speed and executive function11 whereas the Behavior Rating Inventory of Executive Function (BRIEF)[57,1] will be used to measure the Veteran's perception of executive function across nine domains as well as overall executive functioning, behavioral regulation, and metacognition. [57,1] We will also examine testing validity in terms of inadequate effort using the Dot Counting Test2 and response validity using the BRIEF. [57,1]

We define moderately impaired cognitive capacity as having two or more scores falling ≥1 standard deviation below age normed expectations on: the RBANS[58] index scores, DKEFS[11] Color-Word Trials 3 and 4 scale scores, and/or WAIS-IV[59] Digit Span scaled score. Any Veteran with a RBANS Total Scale < 70 will be excluded as this cut-off point suggests likely presence of severe cognitive impairment or major neurocognitive disorder.[60] Any Veteran with DOT (E-score: ≥ 17) or BRIEF-A scores (Negativity ≥ 6; Infrequency ≥ 3; Inconsistency ≥ 8) indicative of questionable testing validity will be excluded. The use of these test performance criteria will identify Veterans who are not employable and are struggling with day to day life requiring assistance with complex Independent Activities of Daily Living due to cognitive impairments.

For Veterans remaining eligible, we seek to link cognitive capacity with cognitive function in daily life as measured with the Assessment of Motor and Process Skills (AMPS) Processing sub-scale, which is a reliable and valid measure of cognitive function[16] defined according to the quality of performance of daily tasks dependent on cognitive abilities (Independent Activities of Daily Living or IADL).[61] The AMPS IADL tasks are selected according to patient profiles and the value placed on the task by the patient, which is determined through a structured interview. We will utilize the streamlined AMPS (AMPS), which will examine the quality of performance of 1

unique IADL while adhering to all administration and scoring procedures. Scoring on the AMPS is not continuous, rather scores may indicate varying levels of impairment depending on the skill of the task examined. All raw AMPS scores are, using AMPS dedicated analytic software, transformed to interval level measures (on a logit scale) and calibrated to neutralize any potential bias due to rater severity or leniency.[62] These calibrations define the boundaries of the five categories of difficulty. We define moderately impaired cognitive function as AMPS Processing sub-scale measures falling below 1.0 logits. This cut-off indicates the Veteran cannot live independently as they have difficulty performing cognitive-based tasks/ADL effectively. [63, 64-66]

This AMPS sub-scale includes IADL items calibrated by difficulty and grouped by five categories (Easiest, Much Easier than Average, Easier than Average, Average and Hardest). The easiest items fall within the 'Uses" domain, which includes tasks requiring use of tools and materials relative to intended uses (e.g., pencil sharpener for pencils but not crayons). The hardest items fall within the 'Accommodates' domain where preventing ineffective task performance requires accommodation (e.g., ironing multiple garments, putting garments away). Across the average difficulty category, there are 45 IADL within five cognitive domains (terminates, navigates, handles, adjusts, continues). The 'terminates' domain, for example, involves appropriate task cessation (e.g., no premature cessation, no persistence) whereas the 'continues' domain involves continuing a task without pauses or delays until task completion.

Veterans who progress to enrollment will create a set of 11 IADL AMPS tasks according to meaningfulness, reported difficulty with performance and as indicated/agreed upon by the researcher according to whether they can be carried out in a clinic setting. To be valid, test items/IADL used in the assessment are not standardized across patients, rather they are selected on the basis of patient profiles and the value/importance placed on the task by the patient. The selected IADL are then setup to accommodate the different ways a person completes the task or equipment/item variations they may use. IADL tasks from this set of 11 tasks will be selected, without replacement, each time the AMPS is administered (Table 2) meaning that a unique task is used with each AMPS administration.

Immediate Effects (ImE) Measures. *For TBI and stroke,* ***magnitude*** *of cognitive gains immediately after a single session of iTBS to the DLPFC are unknown. For healthy controls, however,* ***working memory*** *shows the most consistent and largest effects (g=.938).*[23,67,68] *Thus, we will measure immediate* change in cognitive capacity *according to the domain of working memory* using the **MDS**, which is based on the WAIS-IV Digit Span [69] as it enables repeated administration and has an extensive research base and a structure that lends itself to adaptation with less theoretical likelihood of alternate form reliability issues. To minimize potential reliability issues, the *study Neuropsychologist created* 6 alternate forms that each retain the underlying WAIS-IV Digit Span subtest structure as closely as possible. Each form uses identical instructions, number of practice and test items, and discontinuation and scoring criteria. Each form also includes a unique systematic randomization of digits where number strings follow the same internal structure including minimization of the digits '9' and '5' in a single string (i.e., 'phonetic similarity'), exclusion of repeated digits and '0' for forward/backward trials, consistent placement of repeated digits and '0's as they occur in the original sequencing trials, and introduction of the sequencing trials with a 'no manipulation' item. Further, no more than two sequential digits are used in any trial, and any instances of sequential digits in the original item content are reflected in the adapted trials. As each alternate MDS form will be administered *three times in 30 min intervals,* we will **minimize practice effects** by doing an initial randomization of the ordering for administration of the alternate forms. Thus, each Veteran

across all interventions will be tested with the alternate forms in identical order. Since we are not actually testing and establishing the validity of each form, it is critical that the test conditions be identical across participants. If the alternate forms are not perfectly equivalent, then this identical order allows us to control for this issue across participants.

For measuring immediate changes in cognitive function, we will use the aforementioned **AMPS**. For each of the *three administrations, in 30-min interva*ls, a unique task will be randomly selected (without replacement) from the set of tasks developed during Step 4 (Fig 1). Thus, the same IADL is never repeated for the same Veteran.

Persisting Effects (PE) Measures. This battery includes the same five tests/sub-tests administered during screening (Fig 1, Step-4: AMPS, RBANS, WAIS-IV Digit Span, DKEFS subtests and BRIEF-A). As the BRIEF-A will be re-administered, the study Neuropsychologist will review BRIEF-A scores and, if there are compelling reasons, Veterans with scores suggesting atypical validity will be withdrawn. This battery also includes tests to measure change in mood: Columbia Suicide Severity Rating Scale (C-SSRS) *Beck Anxiety Inventory (BAI),*[71,72] *and the Posttraumatic Stress Disorder Checklist (PCL).*[73] To assess fatigue, we will use the Fatigue Severity Scale (FSS),[74,75] which is a self-report measure of prior-week fatigue during nine activities and current fatigue. To measure behavioral features of agitation, we will use the *Agitated Behavioral Scale (ABS)*. [76-78]

Table 2: Instrumentation: Testing Battery

Immediate Outcome Effects (ImE)	**Hrs/Admin**	**Aims**	**Variable Types**	**# Reps**
AMPS	1.5	1 & 2	Continuous (logit)	3
Modified Digit Span (MDS	0.2	1 & 2	Proportional (% correct)	3
Persisting Effects Testing Battery (PE)	**Hrs/Admin**	**Aims**	**Variable Types**	**# Reps**
Repeatable Battery for Assessment of Neuropsych Status (RBANS)	1.0	2	Continuous (normed score)	5
Weschler Adult Intelligence Scale (WAIS-IV) Digit Span			Proportional (% correct)	5
Delis-Kaplan Executive Functioning System (DKEFS): Color-Word			Continuous (normed score)	5
Behavior Rating Inventory of Executive Function (BRIEF)			Continuous (normed score)	5
AMPS	1.5	2	Continuous (logit)	5
PTSD Checklist (PCL)	0.1	2 & 3	Mean # symptoms/ severity	5
Columbia Suicide Severity Rating Scale (C-SSRS)	0.1	2 & 3	Raw score (Veteran rating)	5
Beck Anxiety Inventory (BAI)	0.1	2 & 3	Raw score (Veteran rating)	5
Agitated Behavior Scale (ABS)	0.1	2 & 3	Raw score (research clinician rating)	5
Fatigue Severity Scale (FSS): Prior Week Daily Living Score	0.1	2 & 3	Raw score (Veteran rating)	5
Fatigue Severity Scale (FSS)L VASF Current Fatigue Rating	0.1	2 & 3	Raw score (Veteran rating)	5

Table 3 Potential Covariates	
Variable/Test	**Operational Definition**
Age at Study Enrollment	Mean or Median **by diagnosis**
Time post neurologic event	2 to 5 yrs. **OR** > 5 to 10 yrs.
# Comorbidities	≤ 3 or > 3
Etiology	**Stroke:** R/L hemisphere **TBI:** DAI + Contusion **OR** DAI + Contusion + Anoxia
Western Aphasia Battery-Screen	Likely **OR** Unlikely to have Aphasia
Boston Assessment of TBI -Lifetime	Lifetime score
Test of Pre-morbid Function	Normed Score
Marijuana	Medical, Recreational, None
Mood: Change in Anxiety	Mean Change
Mood: Change in PTSD symptoms	Mean Change by # and Mean Change in Severity
Mood: Change in Agitation	Mean Change

Covariates. To inform the need for stratified sampling in future research, we will collect a small set of Veteran-specific factors (Table 3) known or strongly thought to influence treatment responsiveness. Given evidence of positive correlations between age and stroke recovery as well as likelihood of further cognitive degradation [79,80] and because prevalence rates dictate use of a wide age range, we will use average age. As comorbid conditions impede recovery or contribute to progressive cognitive degradation for both TBI and stroke, [81,82] we have developed preliminary strata for comorbidities as well as time post event. [83-86] These strata will be revised, as indicated by the sample distribution. For etiology, we will classify stroke as right or left hemisphere and TBI as: injuries resulting in diffuse axonal injury (DAI) and ≥ 1 contusion (e.g., blast, vehicular, assaults) or DAI + ≥ 1 contusion + an anoxic event subsequent to TBI (e.g., respiratory, cardiac). We will include pre-disability intellectual function, as measured with the Test of Premorbid Function, [87] and likelihood of having any type of Aphasia, [88] self-reported marijuana use and Lifetime TBI exposure. [89] Measures obtained during PE testing will also be used to mood changes according to PTSD symptoms, depression, anxiety, and agitation.

****Suitability Measures.*** To advance understanding of each Veteran's perspective of the appropriateness or suitability of that the number and type of tests and number of study-days, Veterans will rate the extent of their agreement to eight statements (Table 4).

Table 4. Indices of Suitability
1. The tests were all appropriate.
2. The number (#) of tests were just right.
3. There were too many tests.
4. I enjoyed participating in this study.
5. I disliked participating in this study.
6. I would recommend the study to a friend.
7. The # of study visits were just right.
8. There were too many study visits**.**

Scale: 1-Completely Disagree; 2- Disagree; 3-Neutral; 4-Agree; 5- Completely Agree

Neuroimaging Data:
Functional MRI measures will be collected at Baseline. Functional MRI measures will include structural imaging, 20 minutes of resting-state fMRI, diffusion tensor imaging (DTI) and an

Arterial Spin Labelling Sequence (ASL). Participants will be in the MRI for approximately 55 minutes. MRI scanning, for all participants, will take place at Northwestern University's CTI in the Olsen Pavilion located at 710 N Fairbanks, Chicago, IL 60611.

fMRI/Image Acquisition: Scanning will take place on a Siemens Prisma 3.0 T MRI scanner equipped with a 64-channel head/neck coil. A high-resolution 3D MP-RAGE T1-weighted sagittal anatomical scan (voxel size = 0.8 mm isotropic resolution; 224 sagittal slices) will be collected for each participant. Resting state BOLD data will be collected using T2* weighted EPI with a TR=0.5s, TE=25ms, flip angle of 48°, and 2mm isotropic voxels and a multiband factor of 8. Rest data will be collected while the subject views a fixation crosshair. The DTI data will use a two shell (64 directions per shell) acquisition with diffusion values of 1000 mm^2/sec. The acquisition will collect 1.5mm isotropic voxels with a TR=4500, TE=62ms and a multiband factor of 4, and 96 slices.

The collection of the fMRI data will be directed by Dr. Todd Parrish. fMRI data collected at CTI will be de-identified and uploaded to Northwestern University Research Image Processing System (NURIPS), an online collaborative research environment for securely storing, managing, analyzing and sharing de-identified medical imaging, associated data (e.g. behavioral), and results from advanced customizable processing pipelines. NURIPS is supported by both Northwestern University IT and Feinberg School of Medicine IT and takes advantage of the NU high performance computing cluster, Quest. NURIPS is a secure environment that supports the latest NU policy and procedures for encryption of data during transit and rest, provides granular project level access controls with varying permissions based on user groups, and allows non-NU collaborators access once they obtain an affiliate NetID. All data are backed up and have restore points that go back for 30 days. Once the data is uploaded to NURIPS, a copy will be downloaded onto Hines VA secure research servers for storage on \\v12.med.va.gov\v12\hin

EEG: For participant safety, all participants will complete a 30-minute baseline EEG sampling. EEG will not be routinely repeated unless clinically indicated. The EEGs will be interpreted by Epileptologists to confirm absence of seizure activity (i.e., epileptiform discharges).

5.6 Data Analysis

Sample Size to Estimate Effect Sizes. Our total sample size of 48 participants is based on 80% power to detect an Effect Size (ES) of .90. For 80% power, sample size per group to detect a small ES (0.35) is 130, for a medium ES (0.60) it is 42 and to detect a large ES (0.90) it is 21 per group. To estimate a large ES of 0.90, 42 subjects are required to achieve 80% power. Thus, we plan for 48 participants and 12% attrition.

Published methods [90] will be used to examine the merits of transdiagnostic sampling (Aim 1i). Specifically, we will use MLM to determine if neurologic diagnosis (stroke, TBI) moderates the effects of the Active intervention (Group 1: n = 24, Active iTBS and Active iTBS + APT; Group 2: n = 24, Placebo iTBS and Placebo iTBS + APT) on Maximum Cognitve Gain (MCG) as measured with the MDS and the AMPS.

For Aim 2, we will inform estimates of effect sizes by testing the idea (2i) that MDS gains and AMPS gains differ for Active iTBS and Active iTBS + APT. As specified in Table 1, we will examine if gains differ in magnitude by computing the MCGs for each outcome (MDS and AMPS) by each intervention. For each outcome, we will compare the Average Active iTBS MCG with the Average Placebo iTBS MCG and the Average Active iTBS + APT MCG with the

Average Placebo iTBS + APT MCG using t-tests for continuous data and z-tests for binary data. Using MLM, we will also determine if Active iTBS is related to more MDS or more AMPS gains. The group (Active iTBS or Placebo iTBS) by time interaction parameter will be used to examine if Active iTBS has a differential trend compared to Placebo iTBS. For 2i, we will also use MLM to identify presence of an additive effect of APT by examining Active iTBS + APT trend lines. For both the AMPS and the MDS outcomes, the group (Active iTBS + APT or Placebo iTBS + APT) by time interaction parameter will be used to examine if the Active iTBS + APT has a differential trend compared to Placebo iTBS + APT. For each intervention we will also determine (2ii) presence of persisting effects of Active iTBS and Active iTBS + APT in the short-term, long-term and cumulatively. Using the PE measures specified in Table 1 and t-tests, we will compare each PE measure for Active iTBS with Placebo iTBS and for Active iTBS + APT with Placebo iTBS + APT. Significant results will be reported. For (2iii), we will use one-tailed t-tests to identify presence of practice effects for MDS and AMPS. We will compare MDS and AMPS average peak gains after Placebo iTBS with average peak gains after Active iTBS. If the average Placebo iTBS peak gain is greater than the average Active iTBS peak gain for either MDS or AMPS, then we will repeat analyses above (for 2i and 2ii) using ImE and PE measures after adjusting them for the detected practice effects.

For Aim 3, we will compute study attrition as percent of participants dropping out after Study-Day 2 and after Study-Day 3. We will examine whether or not these attrition rates differ (3i) by stroke and TBI groups using chi-square. To examine if Veteran's with stroke and TBI have (3ii) different perceptions regarding the suitability of the number and type of tests and number of study-days, we will compare each group's average ratings, by suitability index, using t-tests. To explore the relationship between perceived suitability and fatigue as well as mood (3iii), we will compute Pearson correlations at each of the 5-timepoints (B0 through B4) between average ratings of suitability indices 1 through 3 and averages for each of the two fatigue measures and each of the five mood measures [5x (3x2) + 5x (3x5) = 105 correlations]. We will also compute correlations for average suitability indices 7 through 8 collected on Study-Day 4 (B4) with the averages from that same day for each of the two fatigue measures and each of the five mood measures [1x (2x2) + 1x (2x5) = 14 correlations). We will test the significance of each correlation using Fisher Z test and results will be interpreted accordingly.

Aims 2 and 3 involve multiple comparisons. Bonferroni correction of type I error rate is very conservative, and, at this early research stage, it could mask important findings. Thus, we will control for false discovery rate (FDR)[91,92] using an FDR level of .05.

For Aim 4 we will identify the optimal iTBS Neural Targets using GIMME, which is a directed functional connectivity modeling approach based on iterative model optimization. The optimal brain target is the region that, when modulated, communicates effectively with the neural systems supporting cognition such that it leads to improved cognitive abilities. This target could be a brain region defined at the group level (i.e., generalizable to mild TBI+PTSD population), the subgroup level (specific to mild TBI+PTSD persons with shared features), or at the individual level. GIMME is based on a feed forward method of adding paths among the pre-specified brain Regions of Interest (ROIs) that serve as a fixed anatomical structure. Considering that GIMME models have included 7 to 20 [97,102,103] ROIs, the fixed GIMME anatomical structure will include a set of 12 ROIs implicated in cognition and that serve as nodes in neural networks based on a parcellation atlas[101] will be used in all GIMME models to as the fixed anatomical structure. (Table 5). The threshold for a group-level or sub-group-level pathway connection can be manipulated but we will use 75% as it has been determined to work well.[97] Based on the fixed anatomical structure, GIMME first produces a group-level model of the ROI structure common to at least 75% of the persons in the full dataset/sample. [96,100]

Table 5: ROIs for Fixed Anatomical Structure (i.e., Critical Network Nodes for Most Cognitive Skills)	
Networks	**Network Nodes/Regions of Interest (ROI)**
VAN-Salience	1. right ventral frontal cortex/anterior insula (R VFC/AI) 2. right temporal-parietal junction (R TPJ)
DAN	3. right frontal eye fields (FEF) 4. left FEF 5. right intraparietal sulcus (IPS) 6. left IPS
DMN	7. medial prefrontal cortex (mPFC) 8. posterior cingulate cortex (PCC) (also in FPCN)
FPCN or ECN	9. Left dorsolateral prefrontal cortex (DLPFC) 10. Right DLPFC 11. Parietal association region (PAR) 12. Posterior cuneus (pCUN)

VAN = Ventral Attention Network; including salience network; **DAN =** Dorsal Attention Network; **DMN =** Default Mode Network; **FPCN or ECN =** Frontal Parietal Cortical Network also referred to as the Executive Control Network

After the group model has been developed it is used as a fixed component in the determination of each individual's model that then delineate sub-types/subgroups of persons sharing a common (75% threshold) ROI structure.

The goal is to identify the optimal GIMME brain region (ROI) for stimulating with iTBS. To identify this ROI, we will first identify the best representative pathway (e.g., a pathway is comprised of two ROIs).

To identify the best representative pathway, we will first identify a pathway from each model level (group, sub-types and individual) by using the average the betas (mean betas, μß), for all of the group-level pathways subgroup-level pathways, and individual pathways for each person comprising each model. From all the μß weights from each model level, we will select the pathway with the maximum μß weight. Now that the pathway-level (group, subgroup or individual) has been selected, the path within this collection having the max ß weight will be selected as the pathway most important to cognitive function for this specific participant.

Since we seek to identify one ROI as the optimal iTBS GIMME target and as each pathway is comprised of two ROIs, we will select one of the two ROIs comprising the pathway selected as the most important to cognitive function. This ROI is the ROI with the highest total degree. The graph theory metric of total degree quantifies the sum of in-degree (number of connections coming into the ROI) and out degree (outbound connections). As both in and out degree reflect importance of the ROI to cognition, we will use total degree to select the optimal brain region. If the total degree between the brain regions is equal, we will base the decision on TMS ac-accessibility, Gray Matter Density and/or structural integrity.

Regarding testing Aim 4, the results from above GIMME modeling and decision criteria will, ultimately, test hypothesis that, within our study population of persons **with** moderate cognitive impairment from TBI, there are sub-types/sub-groups of persons with common brain circuitry important to cognition.

Past GIMME work indicates that a minimum of 7 persons with moderate cognitive impairment from TBI will be sufficient to identify an optimal group-level model as well as sub-types/subgroups.[97] That is, 7 participants per diagnosis, here moderate cognitive impairment from TBI, has consistently identified an optimal group-level model as well as subgroups within this diagnosis. Thus, we will strive to enroll at least 7 participants into these optional studies.

AIM 5: Determine immediate gains in working memory and performance of complex IADL after provision of a single session of iTBS targeting to the same location in the L DLPFC after a single session of iTBS targeting the optimal GIMME brain target. We hypothesize that average gains in working memory and functional performance after a single iTBS session site will be

significantly different according to site of stimulation (GIMME site). For each iTBS session, we will compute pre and post iTBS MDS and AMPS scores to be used to compute change in working memory and functional performance of IADL. For each outcome and each treatment site, the mean change will be computed. Using student t-tests, we will compare mean change in working memory and mean change in functional performance between the L DLPFC vs GIMME sites. This will allow us to examine the concept that treatment sites personalized by ROI structure is or is not important for optimizing clinical benefits of iTBS.

5.7 Withdrawal of Subjects

Study participants will be informed during the consent process that their participation in the study protocol is voluntary, and they may choose to discontinue research participation at any time. Discontinuation of research participation will not impact medical care received outside of the research study. Individuals may choose to withdraw from the study for medical or non-medical reasons. If withdrawal from the study occurs during the provision of iTBS, regardless of whether this withdrawal is related or unrelated to the protocol, participants will be evaluated by the study physician and a medically appropriate plan for follow up will be established in a manner that maintains the safety of the research participant. The PI may also choose to withdraw a participant from the study if by the PI's judgment continuation in the study is not in the best interest of the participant for health or safety reasons, non-compliance with study procedures or loss of funding for the project.

Every attempt will be made to retain research participants in this study. Research participants who do not complete their study participation will be replaced only if they withdraw prior to any research procedures past the baseline measures. Unless a research participant revokes his/her consent to use their health information (i.e. revocation of HIPAA Authorization), any data collected prior to study withdrawal will be used in data analysis.

6.0 Reporting

- Theresa Bender Pape will be responsible for training other research staff of the protocol set forth in this IRB application. If unanticipated problem occurs such as deviation to this protocol that involve risks or has the potential to recur, this information will be reported by the investigator, in writing, to the IRB no longer than 5 business days of the investigator or staff becoming aware of the event.

- If the there is an unanticipated, serious adverse event related to this study such as a loss of confidentiality or emotional trauma requiring an intervention (e.g., call to 911, transfer to VA Crisis Hotline), study personnel will notify the IRB within 2 business days but no longer than 5 business days of the investigator or staff becoming aware of the event. Furthermore, if unauthorized access to VA sensitive information related to research including but not limited to protected health information (as defined in 38 CFR 16.102(f)(2)), and confidential information protected by HIPAA, or by Federal records requirements at 38 U.S.C. §§5701, 5705, and 7332, occurs will be reported to the ACOS/Research, Facility Information Security Officer and facility Privacy Officer within 1 hour. Also, if any incident occurs that impacts, inhibits or compromises the network security operations center, this will be reported within 1 hour to the ACOS/Research, Facility Information Security Officer and facility Privacy Officer.

- Any human subject death which is believed to be both unexpected and related or possibly related to participation in research will be verbally reported to the IRB and ACOS/Research within 1 hour and written notification to the IRB within 1 business day. Any SAEs which are believed to be both unexpected and related or possibly related to participation in research will be reported to the IRB within 5 business days. All other AEs will be reported at continuing review. All reports of non-compliance, protocol deviations, information security and privacy incidents will be reported to the IRB within 5 business days.

Five (5) Day Reporting Rules:

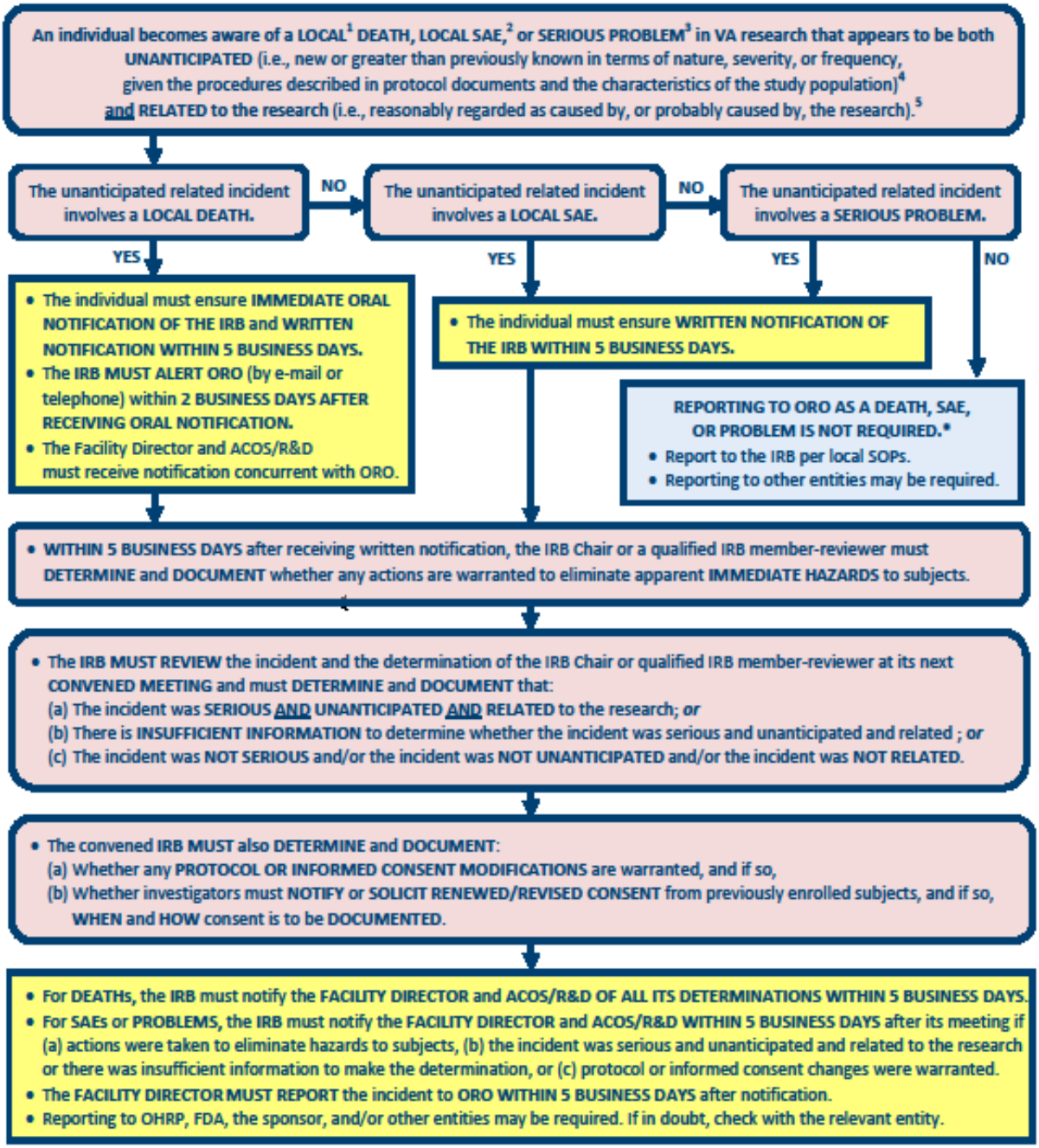
- Reports of local SAEs and unanticipated problems involving risk to subjects or others are reported to IRB no later than 5 business days after becoming aware of the problem.
- VA Policy – Within 5 business days local unanticipated SAE's, unanticipated problems involving risks to subjects or others, and unanticipated plus related deaths must be reported to the IRB. Deaths that are unanticipated problem and related to the research must also be reported to the IRB within 5 business days.
- Local Policy – In addition to VA policy the Hines/FHCC IRB requires the reporting of all local serious adverse events. The IRB recognizes that subjects enrolled in non-interventional minimal risk studies have common life-time events such as hospitalization and early mortality that are unlikely to be unanticipated and are unlikely to be related to the research. In these cases, the requirement for IRB notification may be waived.
- Initial Review – The IRB reviews the protocol and submission documents for reporting of serious adverse events and unanticipated problems involving risks to subjects or others. As with all studies the investigator must follow reporting procedures described in the IRB approved protocol.
- Determinations – Reports are reviewed, findings documented in IRB minutes and written notification provided to the Principal Investigator.
- IRB Reporting to ORO regarding review of serious unanticipated problems and unanticipated SAEs:
- If the convened IRB or the qualified IRB member-reviewer determines that the problem or event is serious and unanticipated and related to the research, the IRB Chair or designee must notify ORO via telephone or e-mail within 48 hours and report the problem or event directly (without intermediaries) to the Facility Director within 5 business days after the determination. The report must be made in writing, with a simultaneous copy to the ACOS/R and the R&D Committee. The Facility Director must report the problem or event to ORO within 5 business days after receiving such notification. A simultaneous determination is required regarding the need for any action necessary to prevent an immediate hazard to subjects including whether or not a protocol or informed consent modification is warranted and if previously enrolled subjects need to be notified.

Non-Five (5) Day Reporting Rules

- Reports of sponsor SAEs, protocol deviations or other issues that do not significantly affect the rights, safety or welfare of subjects, or the integrity of the research data, in the

investigator's judgment. Reports are reviewed, findings documented in IRB minutes and written notification provided to the Principal Investigator.

REPORTING LOCAL DEATHS, LOCAL SERIOUS ADVERSE EVENTS (SAEs), AND SERIOUS PROBLEMS IN VA RESEARCH*



*See 38 CFR 16.103(b)(5)(i); 21 CFR 56.108(b)(1), 312.32(a), & 812.3(s); and VHA Handbook 1058.01 §4g, §4j, §4r, §4t, §4y, & §§6a-7e. This decision chart does not cover other reportable situations (e.g., serious/continuing noncompliance; suspensions/terminations; program changes).

[1] Local means occurring at the reporting facility's own research site(s). [1058.01§4g]

[2] An SAE is an untoward occurrence in human research that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect, or that requires medical, surgical, behavioral, social, or other intervention to prevent such an outcome. [1058.01§4r]

[3] A serious problem is a problem in human research or research information security that may reasonably be regarded as: (1) Presenting a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research personnel, or others, including their rights to privacy and confidentiality of identifiable private information; or (2) Substantively compromising a facility's HRPP or research information security program. [1058.01§4t] *(Examples on ORO's SharePoint site)*

[4] Unanticipated/unexpected refer to an event/problem in human research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol documents and the characteristics of the study population. [§4y]

[5] A related adverse event (AE, §4a), death, or problem is one that may reasonably be regarded as caused by, or probably caused by, the research. [§4j]

[Revised: June 15, 2015]

7.0 Privacy and Confidentiality

All data collected in this protocol, are for research purposes only and only IRB-approved research personnel will have access to this information. Only those investigators and study analysts identified in the study protocol will have access to study data files. There are multiple levels of security to ensure the integrity and confidentiality of all data stored on the system. The computer system operates entirely within the VA network, which is protected by firewalls maintained by the VA Central Office. Cyber security awareness training and privacy training are required annually of all VA employees.

Any breach in security will be reported to ACOS/Research, facility Information Security Officer (ISO), and facility Privacy Officer within one hour. To protect from breach of confidentiality, each Veteran will be assigned a unique identification number by the study personnel and the only place where this identification number will be linked to identifying information (e.g., name, address, phone number, date of birth, social security number) will be on a cross-walk file within secure Hines VA servers that only authorized research staff will be able to access.

All research data is de-identified and stored on a VA protected server (\\v12.med.va.gov\v12\HIN\Research\ResearchLab) with the exception of data collected that will be entered into the electronic REDCap database. This data will be housed on a VA secured server and paper files will be maintained at Hines VA in Bldg 1 in a locked filing cabinet behind a locked door. Only authorized personnel will have access to this data.

All raw and source data will be de-identified and stored in Dr. Bender-Pape's research lab located at Hines VAH (Building 1, Room 317) behind a locked door in locked file cabinets and maintained in compliance set forth by VA and Office of Research Oversight record retention guidelines. Access to the data will be limited to authorized research personnel. If research personnel leave the study, then they will be removed from the study protocol and will not be able to access any research data. Data will be disposed of according to VA policy and in accordance with the applicable VA Records Control Schedule (RCS)

If the 3T Skyra upgrade is not completed at time of study start up, data from each Veteran's T1 anatomical scan will be moved via encrypted USB drive to VA protected server and will be loaded into the Localite TMS Neural Navigator system which is a Magventure compatible and portable neuronavigational system. Based on the T1 image, the left motor cortex will be initially targeted and we will map 5cm anterior of the location to determine motor threshold.

If the 3T Skyra is upgraded at time of study start up, then we will locate the neural target use our Resting State Network Mapping algorithm,[60,93] customized for the Northwestern imaging processing pipeline that we use in our ongoing iTBS studies.[93-95]

Any finding of noncompliance, other deficiencies that substantively compromise the effectiveness of the facility's research information protection program, or suspensions or terminations will be reported to the ACOS/ACME/Research, facility Information Security Officer (ISO), and facility Privacy Officer within 5 days of becoming aware. Any loss of confidentiality falls under immediate reporting requirements and will be reported within the hour of becoming aware.

The information obtained from research analyses may be reported at scientific meetings or in other professional articles, but at no time will the Veteran, his/her family or healthcare surrogate be mentioned by name or any other identifying information.

8.0 Communication Plan

Not applicable

9.0 References

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